Cannabinoid receptor 1 antagonist genistein attenuates marijuana-induced vascular inflammation.

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Public Summary:
Epidemiological studies reveal that marijuana increases the risk of cardiovascular disease (CVD); however, little is known about the mechanism. Delta(9)-tetrahydrocannabinol (Delta(9)-THC), the psychoactive component of marijuana, binds to cannabinoid receptor 1 (CB1/CNR1) in the vasculature and is implicated in CVD. A UK Biobank analysis found that cannabis was an risk factor for CVD. We found that marijuana smoking activated inflammatory cytokines implicated in CVD. In silico virtual screening identified genistein, a soybean isoflavone, as a putative CB1 antagonist. Human-induced pluripotent stem cell-derived endothelial cells were used to model Delta(9)-THC-induced inflammation and oxidative stress via NF-kappaB signaling. Knockdown of the CB1 receptor with siRNA, CRISPR interference, and genistein attenuated the effects of Delta(9)-THC. In mice, genistein blocked Delta(9)-THC-induced endothelial dysfunction in wire myograph, reduced atherosclerotic plaque, and had minimal penetration of the central nervous system. Genistein is a CB1 antagonist that attenuates Delta(9)-THC-induced atherosclerosis.

Scientific Abstract:
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